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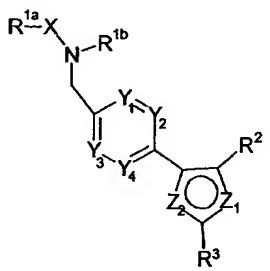
(54) Title: BICYCLIC COMPOUNDS USEFUL AS ANGIOTENSIN II AGONISTS



(I)

(57) Abstract: There is provided compounds of formula I, wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^2 and R^3 have meanings given in the description, and pharmaceutically-acceptable salts thereof, which compounds are useful as selective agonists of the AT2 receptor, and thus, in particular, in the treatment of *inter alia* gastrointestinal conditions, such as dyspepsia, IBS and MOF, and cardiovascular disorders.

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BICYCLIC COMPOUNDS USEFUL AS ANGIOTENSIN II AGONISTS

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, in particular compounds that are angiotensin II (AngII) agonists, more particularly agonists of the AngII type 2 receptor (hereinafter the AT2 receptor), and especially agonists that bind selectively to that receptor. The invention further relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes to their production.

Background and Prior Art

The endogenous hormone AngII is a linear octapeptide (Asp^1-Arg^2-Val^3-Tyr^4-Ile^5-His^6-Pro^7-Phe^8), and is the active component of the renin-angiotensin system (RAS). It is produced by the sequential processing of the pro-hormone angiotensinogen by renin and angiotensin converting enzyme (ACE).

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, body fluid and electrolyte homeostasis. Ang II exerts these physiological actions in many organs including the kidneys, the adrenal glands, the heart, blood vessels, the brain, the gastrointestinal tract and the reproductive organs (de Gasparo *et al*, *Pharmacol. Rev.* (2000) **52**, 415-472).

Two main classes of AngII receptors have been identified, and designated as the type 1 receptor (hereinafter the AT1 receptor) and the AT2 receptor.

The AT1 receptor is expressed in most organs, and is believed to be responsible for the majority of the biological effects of AngII. The AT2 receptor is more prevalent than the AT1 receptor in fetal tissues, the adult ovaries, the adrenal medulla and the pancreas. An equal distribution is reported in the brain and uterus (Ardaillou, *J. Am. Soc. Nephrol.*, **10**, S30-39 (1999)).

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following AngII stimulation, activation of the AT2 receptor has opposing effects to those mediated by the AT1 receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (see de Gasparo *et al, supra*). Further, it seems to play a role in blood pressure control. For example, it has been shown in transgenic mice lacking AT2 receptors that their blood pressure was elevated. Furthermore, it has been concluded that the AT2 receptor is involved in exploratory behaviour, pain sensitivity and thermoregulation.

The expression of AT2 receptors has also been shown to increase during pathological circumstances, such as vascular injury, wound healing and heart failure (see de Gasparo *et al, supra*).

The expected pharmacological effects of agonism of the AT2 receptor are described generally in de Gasparo *et al, supra.*

More recently, AT2 receptor agonists have been shown to be of potential utility in the treatment and/or prophylaxis of disorders of the alimentary tract, such as dyspepsia and irritable bowel syndrome, as well as multiple organ failure (see international patent application WO 99/43339).

International patent application WO 00/68226 and US patent number 6,235,766 disclose compounds comprising substituted imidazolyl groups, which groups are attached, *via* a methylene bridge, to a phenylthiophene moiety, as agonists of angiotensin-(1-7) receptors. International patent application WO 02/072569 discloses similar compounds as agonists of the same receptors. International patent application WO 01/44239 discloses biphenylsulfonamide compounds as combined angiotensin and endothelin receptor antagonists. The use of the compounds as Ang II receptor agonists is neither mentioned nor suggested in any of these documents.

Peptide and non-peptide AT2 receptor agonists, unrelated structurally to those described herein, and potential uses thereof, have been disclosed in, for example, international patent applications WO 00/38676, WO 00/56345, WO 00/09144, WO 99/58140, WO 99/52540, WO 99/46285, WO 99/45945, WO 99/42122, WO 99/40107, WO 99/40106, WO 99/39743, WO 99/26644, WO 98/33813, WO 00/02905 and WO 99/46285; US patent number 5,834,432; and Japanese patent application JP 143695.

AngII antagonists (which bind to the AT1 and/or AT2 receptors) have been disclosed in *inter alia* European patent application EP 512 675; international patent applications WO 94/27597, WO 94/02142, WO 95/23792 and WO 94/03435; and US patent numbers 5,091,390, 5,177,074, 5,412,097, 5,250,521, 5,260,285, 5,376,666, 5,252,574, 5,312,820, 5,330,987, 5,166,206, 5,932,575, 5,444,068, 5,635,525, 5,541,229, 5,864,043 and 5,240,928. AngII agonists, and particularly AT2 receptor agonists, are not contemplated in any of these documents.

US 5,312,820 discloses N-carbamoyl and N-oxycarbonyl derivatives of biphenylmethylamine-based AngII antagonists. The use of these

compounds as AngII agonists, and particularly AT2 receptor agonists, is not contemplated.

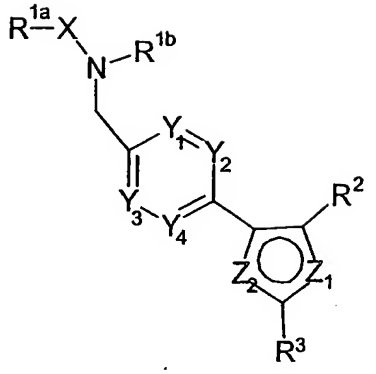
In US 5,240,928 and US 5,330,987, N-cyanophenyl- and N-cyanoheteroaryl-N-carbonyl derivatives of biphenylmethylamines are disclosed generically as potential intermediates useful in the synthesis of *inter alia* quinazolinone- and pyrimidinone-containing Ang II antagonists. The use of these intermediates as pharmaceuticals is neither mentioned nor suggested.

US patent number 5,444,067 discloses compounds comprising a 5,7-dimethyl-2-ethylpyridinoimidazolyl group attached, *via* a methylene bridge, to a phenylthiophene moiety, as AngII agonists. Further, international patent application WO 02/96883 discloses compounds comprising certain monocyclic heterocyclic groups attached, *via* a methylene bridge, to substituted phenylthiophene and biphenyl moieties. The compounds disclosed therein are indicated as AngII agonists and in particular as selective AT2 receptor agonists.

However, there remains a need for effective and/or selective AT2 receptor agonists, which are expected to find utility in *inter alia* the above-mentioned conditions.

Disclosure of the Invention

According to the invention there is provided compounds of formula I,



I

wherein

X represents –O-, –C(O)- or $–S(O)_2$-;

R^{1a} and R^{1b} independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, Ar^1, Het^1, C_{1-3} alkyl-Ar^2, C_{1-3} alkyl-Het^2, C_{1-3} alkoxy-Ar^3 or C_{1-3} alkoxy-Het^3; or, in the case where X represents –C(O)- , R^{1a} may also represent C_{1-6} alkoxy or –O-Ar^4;

Ar^1, Ar^2, Ar^3 and Ar^4 each independently represent a C_{6-10} aryl group, which group is optionally substituted by one or more substituents selected from =O, -OH, cyano, halo, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{11a}$), C_{1-6} alkoxy, phenyl, $-N(R^{12a})R^{12b}$, $-C(O)R^{12c}$, $-C(O)OR^{12d}$, $-C(O)N(R^{12e})R^{12f}$, $-N(R^{12g})C(O)R^{12h}$, $-N(R^{12i})C(O)N(R^{12j})R^{12k}$, $-N(R^{12m})S(O)_2R^{11b}$, $-S(O)_nR^{11c}$, $-OS(O)_2R^{11d}$ and $-S(O)_2N(R^{12n})R^{12p}$;

Het^1, Het^2 and Het^3 each independently represent a four- to twelve-membered heterocyclic group containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group is optionally substituted by one or more substituents selected from =O, -OH, cyano, halo, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{11a}$), C_{1-6} alkoxy, phenyl, $-N(R^{12a})R^{12b}$, $-C(O)R^{12c}$, $-C(O)OR^{12d}$, $-C(O)N(R^{12e})R^{12f}$, $-N(R^{12g})C(O)R^{12h}$, $-N(R^{12i})C(O)N(R^{12j})R^{12k}$, $-N(R^{12m})S(O)_2R^{11b}$, $-S(O)_nR^{11c}$, $-OS(O)_2R^{11d}$ and $-S(O)_2N(R^{12n})R^{12p}$;

R^{11a} to R^{11d} independently represent C_{1-6} alkyl;

R^{12a} to R^{12p} independently represent H or C_{1-6} alkyl;

n represents 0, 1 or 2;

Y_1, Y_2, Y_3 and Y_4 independently represent –CH- or -CF-;

Z_1 represents –CH-, -O-, -S-, -N- or -CH=CH-;

Z_2 represents –CH-, -O-, -S- or –N-;

provided that:

(a) Z_1 and Z_2 are not the same;

(b) when Z_1 represents –CH=CH-, then Z_2 may only represent –CH- or –N-; and

(c) other than in the specific case in which Z_1 represents –CH=CH-, and Z_2 represents –CH-, when one of Z_1 and Z_2 represents –CH-, then the other represents –O- or –S-;

R^2 represents $-S(O)_2N(H)C(O)R^4$, $-S(O)_2N(H)S(O)_2R^4$, $-C(O)N(H)S(O)_2R^4$, or, when Z_1 represents –CH=CH-, R^2 may represent $-N(H)S(O)_2N(H)C(O)R^5$ or $-N(H)C(O)N(H)S(O)_2R^5$;

R^3 represents C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkoxy-C_{1-6}-alkyl;

R^4 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino or di-C_{1-6} alkylamino; and

R^5 represents C_{1-6} alkyl,

or a pharmaceutically-acceptable salt thereof,

which compounds and salts are referred to together hereinafter as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo* or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of

a salt with another counter-ion, for example using a suitable ion exchange resin.

Unless otherwise specified, alkyl groups, and the alkyl parts of alkoxy, alkoxyalkyl, alkylamino, alkyl-aryl, alkyl-heterocyclic groups, alkoxy-aryl and alkoxy-heterocyclic groups, as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic/acyclic. Such alkyl groups, and alkyl parts of alkoxy, alkoxyalkyl, alkylamino, alkyl-aryl, alkyl-heterocyclic, alkoxy-aryl and alkoxy-heterocyclic groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated. Unless otherwise specified, such groups may also be substituted by one or more halo, and especially fluoro, atoms.

For the avoidance of doubt, alkoxy and aryloxy (e.g. –O-Ar^4) groups are attached to the rest of the molecule *via* the oxygen atom in that group, alkylamino groups are attached to the rest of the molecule *via* the nitrogen atom of the amino part of that group, alkoxyalkyl, alkyl-aryl and alkyl-heterocyclic groups are attached to the rest of the molecule *via* the alkyl part of that group, and alkoxy-aryl and alkoxy-heterocyclic groups are attached to the rest of the molecule *via* the alkyl part of the alkoxy part of that group.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention (for example R^{1a} and R^{1b}) may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which R^{1a} and R^{1b}

both represent C_{1-6} alkyl groups, the two alkyl groups in question may be the same of different. Similarly, when aryl and heterocyclic groups are substituted by more than one substituent as defined herein, the identities of the individual substituents are not to be regarded as being interdependent.

C_{6-10} aryl groups include phenyl, naphthyl and the like (preferably phenyl). Preferred optional substituents on aromatic groups include C_{1-3} alkyl groups (such as methyl) or C_{1-3} alkoxy groups.

Het (Het^1 to Het^3) groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het (Het^1 to Het^3) groups may be fully saturated, wholly aromatic, partly aromatic and/or bicyclic in character. Heterocyclic groups that may be mentioned include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzimidazolyl, benzomorpholinyl, benzothiophenyl, chromanyl, cinnolinyl, dioxanyl, furanyl, hydantoinyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, maleimido, morpholinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimindinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiophenyl, thiochromanyl, triazolyl, tetrazolyl and the like. Values of Het^1 that may be mentioned include thiophenyl, furanyl, pyridinyl and thiazolyl. Values of Het^2 that may be mentioned include pyridinyl, furanyl, thiophenyl and thiazolyl. Values of Het^3 that may be mentioned include pyridinyl.

Substituents on Het (Het^1 to Het^3) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point

of attachment of Het (Het^1 to Het^3) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Het (Het^1 to Het^3) groups may also be in the *N*- or *S*-oxidised form.

Preferred ring systems comprising the substituents Y_1, Y_2, Y_3 and Y_4 include phenyl groups. For the avoidance of doubt, the ring systems in compounds of formula I that comprise the groups Z_1 and Z_2, are aromatic in nature. In some instances, for example in cases where one or more of Z_1 and Z_2 represent –CH- or –N- the skilled person will appreciate that an additional H atom may necessarily be bonded to that CH group or N atom, in order to ensure that the rules of valency are adhered to. Preferred ring systems comprising Z_1 and Z_2 include oxazole groups, thiazole groups, phenyl groups, pyridinyl groups, thiophenyl groups and furanyl groups.

In this respect, compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC,

chromatography over silica). All stereoisomers are included within the scope of the invention.

Preferred compounds of the invention include those in which R^{1a} and R^{1b} independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, Ar^1, Het^1, C_{1-3} alkyl-Ar^2, C_{1-3} alkyl-Het^2, C_{1-3} alkoxy-Ar^3 or C_{1-3} alkoxy-Het^3.

It is further preferred that, when X represents –C(O)-, R^{1a} does not represent –O-Ar^4.

More preferred compounds of the invention include those in which:
R^{1a} represents H, C_{1-5} alkoxy, or, more preferably, C_{1-5} alkyl, Ar^1 or Het^1;
Het^1 represents thiophenyl;
R^{1b} represents H or, more preferably, C_{1-4} alkyl, phenyl (optionally substituted by one or more C_{1-2} alkyl groups), C_{1-2} alkylphenyl, C_{1-2} alkyl-Het^2 or C_{1-2} alkoxy-C_{1-2}-alkyl;
Het^2 represents pyridinyl.

More preferred compounds of the invention include those in which:
X represents –O- or, more preferably, –C(O)-;
R^{1a} represents H, C_{1-3} alkoxy (e.g. ethoxy), or, more preferably, C_{1-4} alkyl (e.g. methyl or *n*-butyl), phenyl or thiophenyl;
R^{1b} represents H or, more preferably, C_{1-3} alkyl (e.g. methyl or ethyl), phenyl (optionally substituted by one or more methyl groups), benzyl or methylpyridinyl;
Y_1, Y_2, Y_3 and Y_4 all represent –CH-;
Z_1 represents –CH=CH- or, more preferably, -S-;
Z_2 represents –CH-;
R^2 represents $-S(O)_2N(H)C(O)R^4$;
R^3 represents *n*-butyl or, particularly, *iso*-butyl;

R^4 represents *n*-butyl, *n*-butoxymethyl, *iso*-butoxy and especially, *n*-butoxy.

When X represents –O-, preferred values of R^{1a} include C_{1-3} alkyl, such as methyl. When X represents –C(O)-, preferred values of R^{1a} include H, C_{1-3} alkoxy (e.g. ethoxy), C_{1-4} alkyl (e.g. methyl or *n*-butyl), phenyl or thiophenyl. When X represents $-S(O)_2-$, preferred values of R^{1a} include C_{1-3} alkyl, such as methyl.

When R^2 represents $-S(O)_2N(H)C(O)R^4$, preferred values of R^4 include *n*-butoxymethyl, *iso*-butoxy and especially, *n*-butoxy.

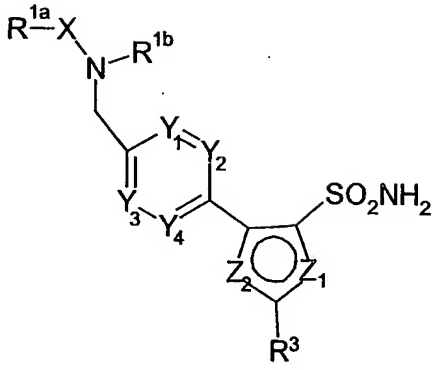
It is preferred that, when R^{1b} represents Ar^1 or Het^1, then those groups are not substituted with a cyano group, e.g. at the 2-position relative to the point of attachment. Further, when R^{1b} represents Ar^1 or Het^1, and Z_1 represents –CH=CH-, it is preferred that Z_2 does not represent –CH-.

More preferred compounds of the invention include the compounds of the examples described hereinafter.

Compounds of formula I may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ or $-S(O)_2N(H)S(O)_2R^4$, and R^4 is as hereinbefore defined, reaction of a compound of formula II,



II

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as hereinbefore defined with a compound of formula III,

$$R^4GL^1 \qquad \text{III}$$

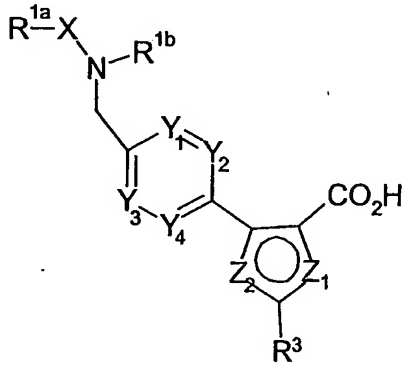
wherein G represents C(O) or $S(O)_2$ (as appropriate), L^1 represents a suitable leaving group, such as halo (e.g. chloro or bromo) and R^4 is as hereinbefore defined, for example at around room temperature or above (e.g. up to 60-70°C) in the presence of a suitable base (e.g. pyrollidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, di-*iso*-propylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, or mixtures thereof) and an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, trifluoromethylbenzene or triethylamine). Preferred base/solvent systems for compounds of formula III in which G is C(O) include pyrollidinopyridine/pyridine, pyrollidinopyridine/triethylamine, dimethylaminopyridine/pyridine or dimethylaminopyridine/triethylamine. Preferred base/solvent systems for compounds of formula III in which G is $S(O)_2$ include NaOH/THF;

(ii) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents C_{1-6} alkoxy-C_{1-6}-alkyl, coupling of a compound of formula II as hereinbefore defined with a compound of formula IV,

$$R^{4a}CO_2H \qquad IV$$

wherein R^{4a} represents C_{1-6} alkoxy-C_{1-6}-alkyl, for example under similar conditions to those described under process step (i) above, in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyl-diimidazole, N,N'-dicyclohexylcarbodiimide, N,N'-disuccinimidyl carbonate, benzotriazole-1-yloxytris(dimethylamino)phosphoniumhexafluorophosphate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosponium hexafluorophosphate or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate), a suitable base (as mentioned in process step (i) above) and an appropriate solvent (as mentioned in process step (i) above);

(iii) for compounds of formula I in which R^2 represents $-C(O)N(H)S(O)_2R^4$ and R^4 is as hereinbefore defined, coupling of a compound of formula V,



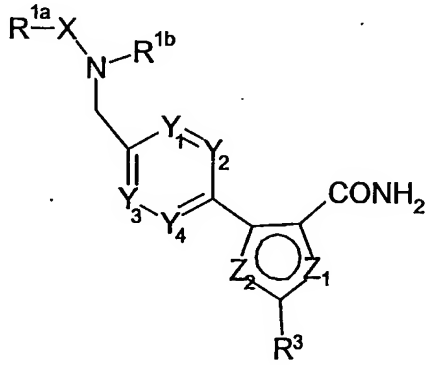
V

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as hereinbefore defined with a compound of formula VI,

$$R^4S(O)_2NH_2 \qquad VI$$

wherein R^4 is as hereinbefore defined, for example in the presence of a suitable coupling reagent (such as those described in process step (ii) hereinbefore), and under similar reaction conditions to those described hereinbefore for preparation of compounds of formula I in which R^4 represents C_{1-6} alkoxy-C_{1-6}-alkyl;

(iv) for compounds of formula I in which R^2 represents $-C(O)N(H)S(O)_2R^4$ and R^4 is as hereinbefore defined, coupling of a compound of formula VII,



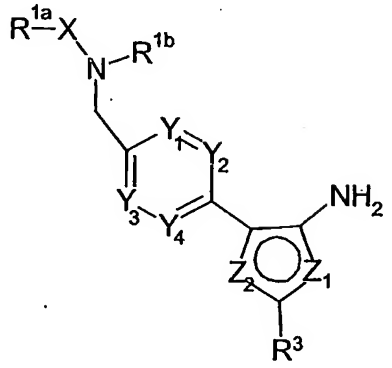
VII

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as hereinbefore defined with a compound of formula VIII,

$$R^4S(O)_2Cl \qquad VIII$$

wherein R^4 is as hereinbefore defined, for example at around 50°C in the presence of a suitable base (e.g. sodium hydride) and an appropriate organic solvent (e.g. THF);

(v) for compounds of formula I in which R^2 represents $-N(H)S(O)_2N(H)C(O)R^5$ and R^5 is as hereinbefore defined, reaction of a compound of formula IX,



IX

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as hereinbefore defined with a compound of formula X,

$$R^5C(O)N(H)S(O)_2Cl \qquad X$$

wherein R^5 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or triethylamine) and a suitable organic solvent (e.g. benzene or dichloromethane);

(vi) for compounds of formula I in which R^2 represents $-N(H)C(O)N(H)S(O)_2R^5$ and R^5 is as hereinbefore defined, reaction of a compound of formula IX as hereinbefore defined with a compound of formula XI,

$$R^5S(O)_2N(H)C(O)OR^x \qquad XI$$

wherein R^x represents C_{1-2} alkyl and R^5 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

(vii) for compounds of formula I in which R^2 represents $-N(H)C(O)N(H)S(O)_2R^5$ and R^5 is as hereinbefore defined, reaction of a compound of formula IX as hereinbefore defined with an isocyanate compound of formula XII,

$$R^5S(O)_2NCO \qquad XII$$

wherein R^5 is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

(viii) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents C_{1-6} alkylamino, reaction of a compound of formula II as hereinbefore defined with an isocyanate compound of formula XIII,

$$R^{4b}NCO \qquad XIII$$

wherein R^{4b} is C_{1-6} alkyl, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or potassium hydroxide and an appropriate organic solvent (e.g. acetone or acetonitrile);

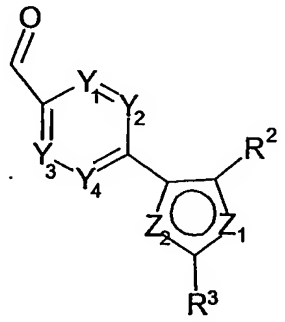
(ix) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents di-C_{1-6} alkylamino, reaction of a corresponding compound of formula I in which R^2 represents

$-S(O)_2N(H)C(O)R^4$ and R^4 represents C_{1-6} alkoxy with an amine of formula XIIIa,

$$R^{4c}N(H)R^{4d} \qquad \text{XIIIa}$$

wherein R^{4c} and R^{4d} independently represent C_{1-6} alkyl, for example at above room temperature (e.g. at between 70°C and 100°C) in the presence of an appropriate organic solvent (e.g. toluene); or

(x) for compounds of formula I in which X represents O, reductive amination of a compound of formula XIV,



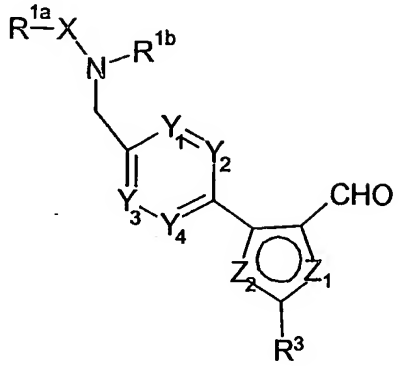
XIV

wherein Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^2 and R^3 are as hereinbefore defined, in the presence of a compound of formula XV,

$$R^{1a}ONHR^{1b} \qquad \text{XV}$$

wherein R^{1a} and R^{1b} are as hereinbefore defined under standard conditions (e.g. in the presence of a suitable organic solvent (e.g. methanol, ethanol, dichloromethane, dichloroethane, tetrahydrofuran or dioxane), and, subsequently, an appropriate reducing agent (e.g. sodium borohydride, sodium cyanoborohydride or $NaBH(OAc)_3$)).

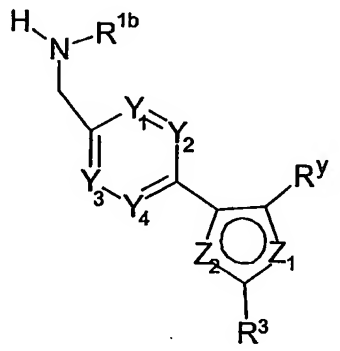
Compounds of formula V may be prepared by oxidation of a compound of formula XVI,



XVI

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as hereinbefore defined, for example under standard oxidation conditions in the presence of a suitable oxidising agent, such as potassium permanganate or chromium (VI) oxide.

Compounds of formulae II, VII, IX and XVI in which X represents –C(O)- or $-S(O)_2-$ may be prepared by reaction of a compound of formula XVII,



XVII

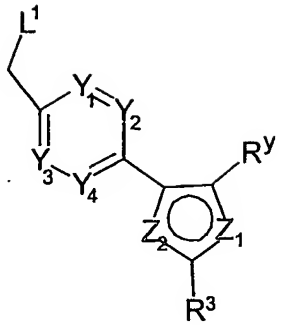
wherein R^y represents $-SO_2NH_2$ (in the case of a compound of formula II), $-CONH_2$ (in the case of a compound of formula VII), $-NH_2$ (in the case of a compound of formula IX), or –CHO (in the case of a compound of formula

XVI), and R^{1b}, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as hereinbefore defined, with a compound of formula XVIII,

$$R^{1a}X^aL^1 \qquad \text{XVIII}$$

wherein X^a represents –C(O)- or –$S(O)_2$- and R^{1a} and L^1 are as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. triethylamine, 4-dimethylaminopyridine, pyrollidinopyridine, diisopropylethylamine or mixtures thereof) and an appropriate organic solvent (e.g. dichloromethane, chloroform, tetrahydrofuran, dioxane or dimethylformamide). Alternatively, compounds of formulae II, VII, IX and XVI in which R^{1a} represents H and X represents –C(O)- may be prepared in this way by reaction of a compound of formula XVII with ammonium formate, for example at above room temperature (e.g. between 80 to 120°C) in the presence of an appropriate organic solvent (e.g. acetonitrile, dioxane, dimethylformamide, ethylene glycol dimethyl ether, 1-methyl-2-pyrrolidinone or dimethylsulphoxide). Preferably compounds of formula XVII are protected at the R^y position prior to carrying out the reaction with the compound of formula XVIII or ammonium formate. Suitable protecting groups for different values of R^y are described hereinafter. If a protected version of a compound of formula XVII is employed, this reaction may be followed by deprotection of the R^y group under standard conditions, for example as described hereinafter.

Compounds of formulae II, VII, IX or XVI in which X represents –C(O)- or –$S(O)_2$- may alternatively be prepared by reaction of a compound of formula XIX,



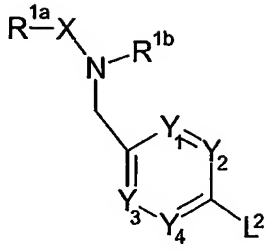
XIX

wherein L^1, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^3 and R^y are as hereinbefore defined (L^1 may, in particular, represent bromo), with a compound of formula XX,

$$R^{1a}X^a\text{-}N(H)\text{-}R^{1b} \qquad XX$$

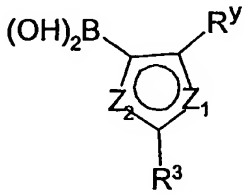
wherein R^{1a}, X^a and R^{1b} are as hereinbefore defined, for example at around or below room temperature in the presence of a suitable base (e.g. potassium hydroxide, potassium *tert*-butoxide, triethylamine or di-*iso*-propylethylamine) and an appropriate organic solvent (e.g. DMSO, DMF, THF or CH_2Cl_2). As with compounds of formula XVII, compounds of formula XIX are preferably protected at the R^y position prior to carrying out the reaction with the compound of formula XX. If a protected version of a compound of formula XIX is employed, this reaction may be followed by deprotection of the R^y group under standard conditions, for example as described hereinafter.

Compounds of formulae II, VII, IX and XVI may alternatively be prepared by reaction of a compound of formula XXI,



XXI

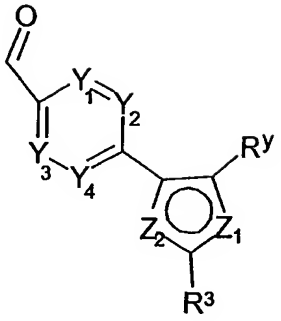
wherein L^2 represents a suitable leaving group, such as trimethylsulphonate, or halo, such as iodo or bromo, and R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3 and Y_4 are as hereinbefore defined, with a compound of formula XXII,



XXII

wherein R^y, R^3, Z^1 and Z^2 are as hereinbefore defined, or a protected derivative thereof, for example in the presence of an appropriate coupling catalyst system (e.g. a palladium catalyst, such as $Pd(PPh_3)_4$ or $Pd(OAc)_2$/ligand (wherein the ligand may be, for example, PPh_3, P(o-Tol)$_3$ or 1,1'-bis(diphenylphosphino)ferrocene)) and a suitable base (e.g. sodium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, triethylamine or di-*iso*-propylamine)), as well as a suitable solvent system (e.g. toluene, ethanol, dimethoxymethane, dimethylformamide, ethylene glycol dimethyl ether, water, dioxane or mixtures thereof). This reaction may be carried out at above room temperature (e.g. at the reflux temperature of the solvent system that is employed).

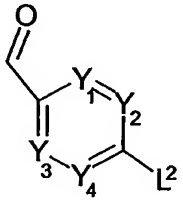
Compounds of formulae II, VII, IX and XVI in which X represents O may alternatively be prepared by reaction of a compound of formula XXIII,



XXIII

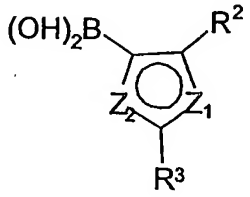
wherein Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^3 and R^y are as hereinbefore defined, or an appropriate protected derivative thereof, with a compound of formula XV as hereinbefore defined, for example under conditions such as those described hereinbefore for preparation of compounds of formula I.

Compounds of formula XIV may be prepared by reaction of a compound of formula XXIV,



XXIV

wherein L^2, Y_1, Y_2, Y_3 and Y_4 are as hereinbefore defined with a compound of formula XXV,



XXV

wherein R^2, R^3, Z_1 and Z_2 are as hereinbefore defined, for example under similar conditions to those decribed hereinbefore for preparation of compounds of formulae II, VII, IX and XVI (third process).

Compounds of formula XV are readily available. For example compounds of formula XV may be prepared by reaction of a compound of formula XXVI,

$$R^{1b}NH_2 \qquad \text{XXVI}$$

wherein R^{1b} is as hereinbefore defined, with an appropriate oxidising agent (for example hydrogen peroxide or *meta*-chloroperbenzoic acid), for example in the presence of a suitable solvent (such as ethanol of methanol), followed by reaction of the intermediate hydroxylamine ($R^{1b}N(H)OH$) with a compound of formula XXVII,

$$R^{1a}L^1 \qquad \text{XXVII}$$

wherein L^1 and R^{1a} are as hereinbefore defined, for example in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, sodium hydroxide or triethylamine) and an appropriate organic solvent (e.g. dioxane, dichloromethane, dimethylformamide and/or acetone). Compounds of formula XV may alternatively be prepared by reaction of an alcohol of formula XXVIII,

$$R^{1a}OH \qquad \text{XXVIII}$$

wherein R^{1a} is as hereinbefore defined, with chloramine (NH_2Cl), for example in the presence of an appropriate base (e.g. sodium hydride, sodium hydroxide or triethylamine) and a suitable solvent (such as diethyl

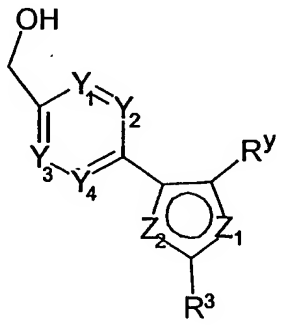
ether, dioxane, dimethylformamide or dichloromethane), followed by reaction of the intermediate oxylamine ($R^{1a}ONH_2$) with a compound of formula XXIX,

$$R^{1b}L^1 \qquad \text{XXIX}$$

wherein L^1 and R^{1b} are as hereinbefore defined, for example in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, sodium hydroxide or triethylamine) and an appropriate organic solvent (e.g. dioxane, dichloromethane, dimethylformamide and/or acetone).

Compounds of formula XVII may be prepared by reductive amination of a compound of formula XXIII as hereinbefore defined, or an appropriate protected derivative thereof, in the presence of an amine of formula XXVI as hereinbefore defined, for example under standard conditions, such as those described hereinbefore for preparation of compounds of formula I.

Compounds of formula XIX may be prepared by conversion of the -OH group in a compound of formula XXX,

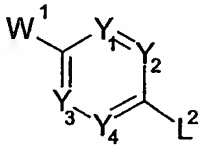


XXX

wherein Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^3 and R^y are as hereinbefore defined, or an appropriate protected derivative thereof, to an appropriate leaving group, L^1 (e.g., in the case where L^1 is bromo, conversion may be carried out by

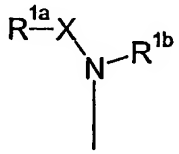
reaction with CBr_4, for example at or around room temperature in the presence of a base (e.g. triphenylphosphine) and a suitable organic solvent (e.g. DMF)).

Compounds of formula XXI may be prepared from compounds of formula XXXI,



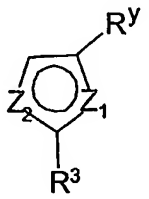
XXXI

wherein W^1 represents –CHO, $–CH_2OH$ or $–CH_2NH_2$ and L^2, Y_1, Y_2, Y_3 and Y_4 are as hereinbefore defined by way of standard techniques, for example by way of known techniques for the conversion of a –CHO, a $–CH_2OH$ or a $–CH_2NH_2$ group into a



group (and in the case of –CHO and $–CH_2OH$ groups analogously to methods described hereinbefore).

Compounds of formula XXII and protected derivatives thereof may be prepared by reaction of a corresponding compound of formula XXXII,



XXXII

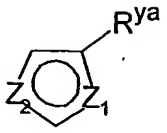
wherein R^y, R^3, Z_1 and Z_2 are as hereinbefore defined, or an appropriate protected derivative thereof, with a reagent system that will enable the introduction of $-B(OH)_2$ into the appropriate ring system. Suitable reagent systems include trialkylborates (e.g. tri-*iso*-propylborate). Such reactions may be carried out, for example, at low temperature (e.g. between -100°C and 0°C, e.g. between -80°C (such as -78°C) and –10°C (such as -20°C)) in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate organic solvent (e.g. THF), followed by acid hydrolysis (e.g. in the presence of dilute HCl).

Compounds of formula XXV may be prepared from corresponding compounds of formula XXII as hereinbefore defined, for example using analogous methods to those described hereinbefore for conversion of the various R^y groups to the relevant R^2 groups (see, for example, processes for the preparation of compounds of formula I).

Compounds of formulae XXIII and XXX may be prepared by reaction of a compound of formula XXXI as hereinbefore defined (in which former case, W^1 represents –CHO and in which latter case, W^1 represents $-CH_2OH$), with a compound of formula XXII as hereinbefore defined, or an appropriate protected derivative thereof, for example under similar conditions to those decribed hereinbefore for preparation of compounds of formulae II, VII, IX and XVI (third process).

Compounds of formula XXXII are available using known techniques. For example:

(a) Compounds of formula XXXII in which R^y represents $-S(O)_2NH_2$, $-C(O)NH_2$ or –CHO, and protected derivatives thereof, may be prepared by reaction of a compound of formula XXXIII,



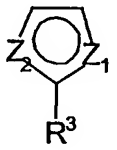
XXXIII

wherein R^{ya} represents $-S(O)_2NH_2$, $-C(O)NH_2$ or –CHO and Z_1 and Z_2 are as hereinbefore defined, or a protected derivative thereof, with a compound of formula XXXIV,

$$R^3L^3 \qquad \text{XXXIV}$$

wherein L^3 represents a suitable leaving group (such as toluenesulphonate, benzenesulphonate, methanesulphonate or halo, such as bromo or iodo) and R^3 is as hereinbefore defined, for example at below room temperature (e.g. between around -35°C and around -85°C), in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

(b) Compounds of formula XXXII in which R^y is $-S(O)_2NH_2$ and N-protected derivatives thereof, may be prepared by reaction of an appropriate compound of formula XXXV,



XXXV

wherein R^3, Z_1 and Z_2 are as hereinbefore defined with an appropriate reagent for introduction of a $-S(O)_2NH_2$ group into the appropriate ring system (for example chlorosulphonic acid, or thionyl chloride in the presence of a suitable strong base (e.g. butyl lithium)), followed by reaction of the resultant intermediate with ammonia, or a

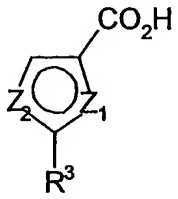
protected derivative thereof (e.g. *tert*-butylamine), under conditions that are well known to those skilled in the art.

(c) Certain protected derivatives (e.g. alkyl, such as C_{1-6} alkyl, for example *tert*-butyl, protected derivatives) of compounds of formula XXXII in which R^y represents $-C(O)NH_2$ may be prepared by reaction of a compound of formula XXXV as hereinbefore defined, with a compound of formula XXXVI,

$$R^ZN=C=O \qquad \text{XXXVI}$$

wherein R^Z represents an appropriate protecting group, such as an alkyl group, including C_{1-6} alkyl, e.g. *tert*-butyl for example at around 0°C, in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

(d) Certain protected derivatives (e.g. alkyl, such as C_{1-6} alkyl, for example *tert*-butyl, protected derivatives) of compounds of formula XXXII in which R^y represents $-C(O)NH_2$ may also be prepared by reaction of a compound of formula XXXVII,



XXXVII

wherein R^3, Z_1 and Z_2 are as hereinbefore defined with a protected (e.g. an (e.g. C_{1-6}) alkyl, such as *tert*-butyl-protected) derivative of ammonia (e.g. *tert*-butylamine) under standard coupling conditions (see, for example, those described hereinbefore for preparation of

compounds of formula I (process step (iii))). Compounds of formula XXXVII are known in the art or may be prepared by way of standard techniques, for example oxidation of a corresponding compound of formula XXXII in which R^y is -CHO e.g. under those conditions described hereinbefore for preparation of compounds of formula V.

(e) Compounds of formula XXXII in which R^y is –CHO, Z_1 represents –CH=CH- and Z_2 represents –CH-, and protected derivatives thereof, may be prepared by reaction of a compound of formula XXXV in which Z_1 represents –CH=CH- and Z_2 represents –CH$_2$ with an appropriate reagent system for the introduction of an aldehyde group into the benzene ring (e.g. $TiCl_4/CHCl_3$, $SnCl_4/CH_2Cl_2$ or 1,3,5,7-azaadamantane/TFA) under standard reaction conditions, followed by (if appropriate) protection of the resultant benzaldehyde under standard conditions.

(f) Compounds of formula XXXII in which R^y is –NH_2, Z_1 represents –CH=CH- and Z_2 represents –CH-, and N-protected derivatives thereof, may be prepared by nitration of a compound of formula XXXV in which Z_1 represents –CH=CH- and Z_2 represents –CH-, followed by reduction of the resultant nitrobenzene and (if appropriate) protection of the resultant aminobenzene, all of which steps may be carried out under standard conditions.

Compounds of formulae III, IV, VI, VIII, X, XI, XII, XIII, XIIIa, XVIII, XX, XXIV, XXVI, XXVII, XXVIII, XXIX, XXXI, XXXIII, XXXIV, XXXV and XXXVI are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance

with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include sulphonamido, amido, amino and aldehyde. Suitable protecting groups for sulphonamido, amido and amino include *tert*-butyloxycarbonyl, benzyloxycarbonyl, 2-trimethylsilylethoxycarbonyl (Teoc) or *tert*-butyl. Suitable protecting groups for aldehyde include alcohols, such as methanol or ethanol, and diols, such as 1,3-propanediol or, preferably, 1,2-ethanediol (so forming a cyclic acetal).

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques (e.g. using trifluoroacetic acid, sulfuric acid, toluenesulfonic acid or boron trichloride).

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient,

manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Medical and Pharmaceutical Uses

Compounds of the invention are useful because they possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, compounds of the invention are agonists of AngII, more particularly, are agonists of the AT2 receptor, and, especially, are selective agonists of that sub-receptor, for example as may be demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in those conditions in which endogenous production of AngII is deficient and/or where an increase in the effect of AngII is desired or required.

The compounds of the invention are further expected to be useful in those conditions where AT2 receptors are expressed and their stimulation is desired or required.

The compounds of the invention are further indicated in the treatment of conditions characterised by vasoconstriction, increased cell growth and/or differentiation, increased cardiac contractility, increased cardiovascular hypertrophy, and/or increased fluid and electrolyte retention.

The compounds of the invention are further indicated in the treatment of stress-related disorders, and/or in the improvement of microcirculation and/or mucosa-protective mechanisms.

Thus, compounds of the invention are expected to be useful in the treatment of disorders, which may be characterised as indicated above, and which are of, for example, the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system and the central nervous system (CNS).

Disorders of the gastrointestinal tract that may be mentioned include oesophagitis, Barrett's oesophagus, gastric ulcers, duodenal ulcers, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pancreatitis, hepatic disorders (such as hepatitis), gall bladder disease, multiple organ failure (MOF) and sepsis. Other gastrointestinal disorders that may be mentioned include xerostomia, gastritis, gastroparesis,

hyperacidity, disorders of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion and Sjögren's syndrome.

Disorders of the respiratory tract that may be mentioned include inflammatory disorders, such as asthma, obstructive lung diseases (such as chronic obstructive lung disease), pneumonitis, pulmonary hypertension and adult respiratory distress syndrome.

Disorders of the kidneys that may be mentioned include renal failure, nephritis and renal hypertension.

Disorders of the eyes that may be mentioned include diabetic retinopathy, premature retinopathy and retinal microvascularisation.

Disorders of the female reproductive system that may be mentioned include ovulatory dysfunction.

Cardiovascular disorders that may be mentioned include hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post-balloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, angina, cardiac arrhythmias, claudicatio intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic lesions, erectile dysfunction and neointima proliferation.

Disorders of the CNS that may be mentioned include cognitive dysfunctions, dysfunctions of food intake (hunger/satiety) and thirst, stroke, cerebral bleeding, cerebral embolus and cerebral infarction.

Compounds of the invention may also be useful in the modulation of growth metabolism and proliferation, for example in the treatment of hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, the healing of ulcers, inhibition of adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer (e.g. in the gastrointestinal tract, lung cancer, etc), apoptosis, tumours (generally) and hypertrophy, diabetes, neuronal lesions and organ rejection.

The compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a condition in which endogenous production of AngII is deficient, and/or a condition where an increase in the effect of AngII is desired or required, and/or a condition where AT2 receptors are expressed and their stimulation is desired or required, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

When the condition to be treated is multiple organ failure, preferred routes of administration are parenteral (e.g. by injection). Otherwise, the preferred route of administration for compounds of the invention is oral.

The compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be administered in combination with other AT2 agonists that are known in the art, as well as in combination with AT1 receptor antagonists that are known in the art, such as losartan, or in combination with an inhibitor of angiotensin converting enzyme (ACE).

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention; and

(B) an AT1 receptor antagonist, or an ACE inhibitor,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of compound of the invention in conjunction with an AT1 receptor antagonist, or an ACE inhibitor, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises compound of the invention, and at least one comprises AT1 receptor antagonist, or ACE

inhibitor, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including compound of the invention and AT1 receptor antagonist or ACE inhibitor).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention and an AT1 receptor antagonist, or an ACE inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, or an ACE inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Depending upon the disorder and patient to be treated and the route of administration, the compounds of the invention may be administered at varying doses.

Although doses will vary from patient to patient, suitable daily doses are in the range of about 1 to 1000 mg per patient, administered in single or multiple doses. More preferred daily doses are in the range 2.5 to 250 mg per patient.

Individual doses of compounds of the invention may be in the range 1 to 100 mg.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention have the advantage that they bind selectively to, and exhibit agonist activity at, the AT2 receptor. By compounds which "bind selectively" to the AT2 receptor, we include that the affinity ratio for the relevant compound (AT2:AT1) is at least 5:1, preferably at least 10:1 and more preferably at least 20:1.

The compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art.

Biological Tests

The following test procedures may be employed.

Test A

Receptor Binding Assay using Rat Liver Membrane AT_1 Receptor

Rat liver membranes were prepared according to the method of Dudley *et al* (*Mol. Pharmacol.* (1990) 38, 370). Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [^{125}I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 4 × 2 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a gamma counter. The characteristics of the Ang II binding AT_1 receptor were determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]AngII. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [^{125}I]AngII. The dissociation constant (K_d = 1.7 ± 0.1 nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.

Test B

Receptor Binding Assay using Porcine Myometrial Membrane AT_2 Receptor

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen *et al* (*Clin. Exp. Pharm. Phys.* (1997) 24, 309). Any possible interference that may be exhibited by binding of compound to AT_1 receptors was blocked by addition of 1 μM of a selective AT1 inhibitor. Binding of [^{125}I]Ang II to membranes was conducted in a final volume of

0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [^{125}I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured using a gamma counter. The characteristics of the Ang II binding AT_2 receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]Ang II. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [^{125}I]Ang II. The dissociation constant (K_d = 0.7 ± 0.1 nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate .

Test C

Duodenal Mucosal Alkaline Secretion Assay

Compounds were exposed to the duodenal mucosa in barbiturate-anaesthetised rats prepared for *in situ* titration of duodenal mucosal alkaline secretion, according to the methodology described by Flemström *et al* in *Am. J. Physiol.* (1982) **243**, G348.

The invention is illustrated by way of the following examples.

Preparation A

3-(4-Formylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

(a) *N*-*tert*-Butylthiophene-2-sulfonamide

Thiophene-2-sulfonyl chloride (15 g, 0.082 mol) was dissolved in $CHCl_3$ (200 mL) under N_2 atmosphere and then cooled to 0°C. *tert*-Butylamine (25.9 mL, 0.246 mol) dissolved in $CHCl_3$ (50 mL) was then added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at room temperature and then at reflux for 10 min. Toluene (700 mL) was added and the organic phase was washed with water (3 x 50 mL), dried, and concentrated *in vacuo*. The sub-title product was used without further purification in the next step.

^{1}H NMR ($CDCl_3$) δ 7.60(1H, dd, J=1.3, 3.8 Hz), 7.53(1H, dd, J=1.3, 5.0 Hz), 7.02(1H, dd, J=5.0, 3.8 Hz), 5.13(1H, m), 1.24 (9H, m)

^{13}C NMR ($CDCl_3$) δ 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(b) 5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-sulfonamide

N-*tert*-Butylthiophene-2-sulfonamide (10 g, 0.046 mol, see step (a) above) was dissolved in THF (85 mL) under N_2 and then cooled to –78°C. *n*-BuLi (1.6 M, 76.9 mL, 0.12 mol) was added *via* a syringe. The reaction mixture was stirred at –78°C for 30 min. and then at –40°C for 2 h. Iodo-2-methylpropane (10.5 mL, 0.09 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) and extracted with EtOAc. The combined organic phase was washed with brine and dried and concentrated *in vacuo*. The crude product was purified on column chromatography (hexanes:EtOAc (10:1)) to give the sub-title compound in 55% yield (7.0 g, 0.025 mol).

^{1}H NMR ($CDCl_3$) δ 7.43(1H, d, J= 3.6 Hz), 6.67(1H, d, J=3.8 Hz), 4.83(1H, m), 2.67(2H, d, J=7 Hz), 1.88 (1H, m), 1.26(9H, m), 0.93(6H, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(c) 5-*iso*-Butyl-2-(N-*tert*-butylaminosulfonyl)thiophene-3-boronic acid

5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-sulfonamide (10.6 g, 0.039 mol, see step (b) above) was dissolved in THF (165 mL) under N_2 and then cooled to –78°C. *n*-BuLi (1.6 M, 60.19 mL, 0.096 mol) was added *via* a syringe. The reaction mixture was stirred at –20°C for 4 h. The tri-*iso*-propylborate (13.3 mL, 0.058 mol) was then added *via* a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The product may be used without further purification.

MS(ESI^+) m/z: 236.8

(d) 3-(4-Formylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

Palladium acetate (69.6 mg, 0.31 mmol) and triphenylphosphine (0.33 g, 1.24 mmol) in THF (5 mL) were stirred for 30 min under N_2(g). The solvent was removed *in vacuo* and the residue was dissolved in DME (5 mL). The catalyst was then transferred into a nitrogen-flushed mixture of 5-*iso*-butyl-2-(N-*tert*-butylaminosulfonyl)-thiophene-3-boronic acid (1.11 g, 3.13 mmol, based on 90% purity, see step (c) above), 4-bromobenzaldehyde (1.45 g, 7.84 mmol) and potassium carbonate (1.73 g, 12.5 mmol) in a solvent mixture of DME (10 mL), ethanol (3 mL), and water (2 mL). After stirring for 20 h at reflux under a N_2 atmosphere, the reaction mixture was diluted with 1M NaOH solution (20 mL) followed by ethyl acetate (70 mL). The organic layer was washed with water, and brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and the residue subjected to flash

chromatography (20% ethyl acetate in petroleum ether, 230-400 mesh) to afford the title compound as colourless solid (0.76 g, 64%).

IR (neat, cm^{-1}) v 3284, 2963, 1702, 1606

^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.01 (s, 9H), 1.94 (m, 1H), 2.68 (d, J = 6.6 Hz, 2H), 4.24 (s, 1H), 6.78 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 6.6 Hz, 2H), 10.04 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 22.1, 29.6, 30.5, 39.1, 54.7, 128.7, 129.6, 129.8, 135.7, 137.5, 141.0, 141.8, 149.0, 191.8

MS (ESI^+) m/z: 379.9 (M^+ +1)

Anal. Calcd for $C_{19}H_{25}NO_3S_2$: C, 60.13; H, 6.64, N, 3.69; O, 12.65; S, 16.9; Found C, 59.9; H, 6.6; N, 3.6; O, 12.4; S, 16.8

Examples 1 to 12

General Procedure

Step 1: The appropriate amine (1.1 eqv., 0.09 mmol, see below) was added to a solution of 3-(4-formylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (30 mg, 0.08 mmol, see Preparation A above) in methanol (1.5 mL) in a sample vial (5 mL size). After being stirred for 2 h, sodium borohydride (6.1 mg, 0.16 mmol) was added and the stirring continued for 2 h. The mixture was acidified with dilute HCl (5 N, 0.1 mL), stirred for 10 min, neutralised with saturated $NaHCO_3$ solution (~0.5 mL) and diluted with ethyl acetate (10 mL). The contents were poured into diatomaceous earth (liquid-liquid extraction cartridge) in a polypropylene column (packed for 1.5 cm, 24 mL size) and eluted with ethyl acetate (30 mL). Concentration under vacuum afforded the crude product.

Step 2: The product from step 1 was dissolved in dry DCM (1.5 mL) in a sample vial (5 mL size). Triethylamine (0.033 mL, 0.24 mmol), DMAP (1 mg, 0.008 mmol) and the appropriate acid chloride or alkyl chloroformate

(2 eqv., 0.16 mmol, see below) were then added sequentially. The sample vial was tightly closed. The mixture was stirred overnight, quenched with aqueous saturated $NaHCO_3$ solution (0.5 mL), stirred for 30 min, and filtered through diatomaceous earth (packed for 1.5 cm in the column of 24 mL capacity) on elution with DCM (30 mL). Concentration *in vacuo* afforded the crude product.

Step 3: The mixture of the product from step 2 and anisole (~2 drops) in trifluoroacetic acid (1.5 mL) in a sample vial (5 mL size) was stirred at 30°C overnight. After the removal of the solvent *in vacuo*, the residue was dissolved in acetonitrile (2 mL) and evaporated (2 x).

Step 4: To a mixture of the product from step 3 in dry DCM (1.5 mL), pyrrollidinopyridine (17.8 mg, 0.12 mmol) and triethylamine (0.5 mL, 0.36 mmol), *n*-butyl chloroformate (0.04 mL, 0.3 mmol) were sequentially added. The solution was stirred for 12 h, concentrated *in vacuo* and the crude product purified by LCMS (30% acetonitrile to pure acetonitrile, reverse phase) to afford the title products indicated below:

Example 1

N-Butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-benzylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using benzylamine and acetyl chloride. The crude product from the final step was purified by LCMS (25% aqueous acetonitrile to pure acetonitrile, reverse phase) to afford a colourless solid (30 mg, 68%).

IR (neat, cm^{-1}) ν 2955, 1747, 1629, 1451

^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 0.98 (d, J = 7.4 Hz, 6H), 1.25 (m, 2H), 1.49 (m, 2H), 1.94 (m, 1H), 2.2 (d, 3H, J = 3.63 Hz), 2.66- 2.75

(m, 2H), 3.98- 4.08 (m, 2H), 4.46- 4.60 (m, 4H), 6.75 (d, 1H, J = 8.58 Hz), 7.14- 7.51 (m, 9H), 8.25 (brd, 1H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.7, 21.5, 22.2, 29.6, 30.4, 30.5, 39.3, 48.0, 50.5, 51.1, 66.7, 66.8, 126.3, 127.4, 127.7, 128.0, 128.3, 128.6, 129.0, 129.1, 129.4, 129.5, 130.7, 133.2, 133.4, 136.0, 136.9, 137.0, 137.6, 145.9, 146.1, 150.3, 151.3, 151.5, 171.4, 171.6

MS (ESI^+) m/z: 557.3 (M^+ +1)

Anal. Calcd for $C_{29}H_{36}N_2O_5S_2$: C, 62.56; H, 6.52; N, 5.03; Found C, 62.8; H, 6.7; N, 5.0

Example 2

N-Butyloxycarbonyl-3-[4-(*N*-benzylpentylamidomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using benzylamine and valeroyl chloride. The crude product from the final step was purified by LCMS (30% aqueous acetonitrile to pure acetonitrile, reverse phase) to afford a colourless solid (26 mg, 55%).

IR (neat, cm^{-1}) ν 2959, 2871, 1748, 1626, 1453

^{1}H NMR ($CDCl_3$) δ 0.83-1.03 (m, 12H), 1.17-1.44 (m, 6H), 1.68 (m, 2H), 1.95 (m, 1H), 2.44 (dt, J = 1.25, 8.3 Hz, 2H), 2.66-2.74 (m, 2H), 4.05 (q, J = 5.3 Hz, 2H), 4.43-4.68 (m, 4H), 6.76 (d, J = 7.9 Hz, 1H), 7.1-7.50 (m, 9H), 7.60-7.95 (brs, 1H)

^{13}C NMR ($CDCl_3$) δ 13.6, 13.9, 18.7, 22.2, 22.5, 27.5, 30.4, 30.5, 33.0, 39.3, 48.1, 49.7, 50.4, 66.8, 66.9, 126.4, 127.4, 127.7, 128.0, 128.3, 128.6, 128.9, 129.1, 129.5, 130.6, 133.0, 133.3, 136.3, 137.2, 137.3, 138.0, 146.1, 146.2, 150.2, 151.4, 151.6, 173.9, 174.1

MS (ESI^+) m/z: 598.8 (M^+ +1)

Anal. Calcd for $C_{32}H_{42}N_2O_5S_2$: C, 64.18; H, 7.07; N, 4.68; Found C, 63.8; H, 7.0; N, 4.70

Example 3

N-Butyloxycarbonyl-3-[4-(*N*-*p*-tolylbenzylamidomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using *p*-tolylamine and benzoyl chloride. The crude product from the final step was purified by LCMS (45% aqueous acetonitrile to pure acetonitrile, reverse phase) to afford a colourless solid (49 mg, 92%).

IR (neat, cm^{-1}) ν 2960, 1748, 1628, 1511, 1447

^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H), 1.24 (m, 2H), 1.48 (m, 2H), 1.93 (m, 1H), 2.23 (s, 3H), 2.69 (d, J = 6.9 Hz, 2H), 3.99 (t, J = 6.6 Hz, 2H), 5.12 (s, 2H), 6.76 (s, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 7.1-7.24 (m, 3H), 7.31-7.44 (m, 6H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.7, 20.9, 22.3, 30.4, 39.5, 53.8, 66.8, 127.4, 127.8, 128.2, 128.8, 129.0, 129.3, 129.7, 133.0, 135.7, 136.7, 138.2, 140.8, 146.1, 146.9, 151.4, 170.6

MS (ESI^+) m/z: 618.8 (M^+ +1)

Anal. Calcd for $C_{34}H_{38}N_2O_5S_2$: C, 65.99; H, 6.19; N, 4.53 Found C, 65.8; H, 6.4; N, 4.3

Example 4

N-Butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-*p*-tolylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using *p*-tolylamine and acetyl chloride. The crude product from the final step was purified by LCMS (40% aqueous acetonitrile to pure acetonitrile, reverse phase) to afford a colourless solid (44 mg, 68%).

IR (neat, cm^{-1}) ν 2960, 1747, 1636, 1513, 1465

^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H), 1.24 (m, 2H), 1.48 (m, 2H), 1.82-12.1 (m, 4H), 2.33 (s, 3H), 2.69 (d, J = 7.26 Hz, 2H), 4.02 (t, J = 6.6 Hz, 2H), 4.83 (s, 2H), 6.76 (s, 1H), 6.88 (d, J = 8.3 Hz,

2H), 7.13 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 8.36 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.8, 21.1, 22.2, 22.5, 29.7, 30.5, 39.3, 52.6, 66.7, 127.8, 128.7, 128.9, 129.3, 130.2, 130.9, 133.1, 138.0, 140.0, 146.0, 150.3, 151.2, 171.1

MS (ESI$^+$) m/z: 556.8 (M^+ +1)

Anal. Calcd for $C_{29}H_{36}N_2O_5S_2$.1/2 H_2O: C, 61.6; H, 6.6; N, 4.9 Found: C, 61.7; H, 6.5; N, 4.8

Example 5

N-Butyloxycarbonyl-3-{4-[*N*-(pyridin-3-ylmethyl)benzylamidomethyl]-phenyl}-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using 3-picolylamine and benzoyl chloride. The crude product from the final step was purified by LCMS (45% aqueous acetonitrile to pure acetonitrile, reverse phase) to afford a colourless solid (45 mg, 92%).

IR (neat, cm^{-1}) ν 2959, 1740, 1635, 1457, 1410

^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 0.97 (d, J = 6.6 Hz, 6H), 1.30 (m, 2H), 1.55 (m, 2H), 1.92 (m, 1H), 2.68 (d, J = 6.9 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 4.58- 4.82 (m, 4H), 6.6 (br s, 1H), 6.9- 7.54 (m, 11H), 8.23-8.43 (m, 2H)

^{13}C NMR ($CDCl_3$) δ 13.7, 18.9, 22.2, 30.5, 30.7, 39.2, 48.1, 50.9, 53.5, 55.9, 65.9, 123.5, 123.9, 126.1, 126.5, 128.3, 128.8, 129.3, 129.7, 133.0, 134.1, 134.8, 135.9, 136.7, 139.9, 144.4, 146.5, 147.5, 147.3, 148.3, 148.4, 150.3, 152.0, 172.1

MS (ESI$^+$) m/z: 620.1 (M^+ +1)

Anal. Calcd for $C_{33}H_{37}N_3O_5S_2$: C, 63.95; H, 6.02; N, 6.78 Found C, 63.6; H, 6.2; N, 6.4

Example 6

N-Butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-pyridin-3-ylmethylaminomethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using 3-picolylamine and acetyl chloride. The crude product from the final step was purified by LCMS (45% aqueous acetonitrile to 90% acetonitrile, reverse phase) to afford a colourless syrup (38 mg, 86%).

IR (neat, cm^{-1}) ν 2960, 1742, 1650, 1429

^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 6H), 1.26 (m, 2H), 1.53 (m, 2H), 1.93 (m, 1H), 2.27 (m, 3H), 2.68 (d, J = 6.9 Hz, 2H), 4.07 (m, 2H), 4.49 (s, 2H), 4.65 (t, J = 6.9 Hz, 2H), 6.68 (m, 1H), 6.93- 7.36 (m, 6H), 7.61- 8.45 (m, 2H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.8, 22.2, 30.4, 30.6, 39.2, 48.2, 50.8, 52.2, 54.9, 65.8, 123.6, 127.2, 128.0, 128.5, 129.3, 129.7, 132.0, 132.5, 133.1, 133.6, 133.9, 134.7, 136.1, 136.4, 138.7, 139.9, 144.3, 145.0, 146.2, 147.4, 147.9, 148.2, 150.3, 151.6, 152.0, 170.6, 170.8

MS (ESI^+) m/z: 558.2 (M^+ +1)

Anal. Calcd for $C_{28}H_{35}N_3O_5S_2$. ½ H_20: C, 59.30; H, 6.4; N, 7.4 Found C, 59.5; H, 6.1; N, 7.4

Example 7

N-Butyloxycarbonyl-3-[4-(N-methylpentylamidomethyl)phenyl]-5-iso-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using methylamine and valeroyl chloride. The crude product from the final step was purified by LCMS (30% aqueous acetonitrile to 85% acetonitrile, reverse phase) to afford a colourless syrup (26 mg, 63%).

IR (neat, cm^{-1}) ν 2959, 1747, 1628, 1466

^1H NMR ($CDCl_3$) δ 0.82-1.02 (m, 12H), 1.17- 1.56 (m, 6H), 1.66 (m, 2H), 1.93 (m, 1H), 2.38 (m, 2H), 2.65- 2.74 (d, J = 6.9 Hz, 2H), 2.95 (m, 3H),

4.02 (t, J = 6.6 Hz, 2H), 4.57 (s, 2H), 6.75 (m, 1H), 7.22 (m, 2H), 7.44 (m, 2H)

^{13}C NMR ($CDCl_3$) δ 13.6, 13.9, 18.7, 22.2, 22.6, 27.2, 27.5, 30.4, 30.5, 32.9, 33.2, 33.9, 35.2, 39.3, 50.6, 53.1, 66.7, 66.8, 126.2, 127.7, 129.1, 129.4, 130.7, 133.0, 133.3, 137.3, 138.0, 146.1, 150.3, 151.3, 151.5, 173.6, 173.7

MS (ESI^+) m/z: 522.9 (M^+ +1)

Anal. Calcd for $C_{26}H_{38}N_2O_5S_2$: C, 59.74; H, 7.33; N, 5.36 Found C, 59.8; H, 7.5; N, 5.5

Example 8

N-Butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using methylamine and acetyl chloride. The crude product from the final step was purified by LCMS (35% aqueous acetonitrile to 85% acetonitrile, reverse phase) to afford a colourless syrup (19 mg, 50%).

IR (neat, cm^{-1}) ν 2960, 1746, 1628, 1466

^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.3 Hz, 3H), 0.92 (d, J = 6.6 Hz, 6H), 1.18 (m, 2H), 1.44 (m, 2H), 1.87 (m, 1H), 2.09 (m, 3H), 2.65 (m, 2H), 2.90 (m, 3H), 3.97 (m, 2H), 4.52 (m, 2H), 6.69 (m, 1H), 7.17 (m, 2H), 7.39 (m, 2H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.8, 21.4, 21.7, 22.2, 30.4, 30.5, 33.8, 35.8, 39.3, 50.5, 54.0, 66.7, 66.8, 126.2, 127.8, 129.2, 129.4, 129.5, 130.9, 133.2, 133.5, 137.0, 137.7, 146.0, 150.5, 151.2, 151.5, 171.2

MS (ESI^+) m/z: 480.8 (M^+ +1)

Anal. Calcd for $C_{23}H_{32}N_3O_5S_2$: C, 57.47; H, 6.71; N, 5.83 Found: C, 57.0; H, 6.7; N, 5.8

Example 9

N-Butyloxycarbonyl-3-[4-(*N*-ethyl-thiophenecarbonylaminomethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using ethylamine and thiophenecarboxyl chloride. The crude product from the final step was purified by LCMS (45% aqueous acetonitrile to 90% acetonitrile, reverse phase) to afford a colourless syrup (20 mg, 45%).

IR (neat, cm^{-1}) ν 2960, 1748, 1604, 1436

^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 0.99 (d, J = 6.6 Hz, 6H,), 1.24 (m, 5H), 1.50 (m, 2H), 1.95 (m, 1H), 2.71 (d, J = 7.3 Hz, 2H), 3.58 (q, J = 6.9 Hz, 2H), 4.03 (t, J = 6.6 Hz, 2H), 6.78 (s, 1H), 7.02 (t, J = 4.1 Hz, 1H), 7.29- 7.50 (m, 6H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.7, 22.2, 30.5, 39.3, 66.9, 126.9, 127.1, 128.6, 129.1, 129.3, 130.6, 133.2, 137.8, 146.1, 150.0, 151.6, 164.6

MS (ESI^+) m/z: 563.2 (M^+ +1)

Anal. Calcd for $C_{27}H_{34}N_2O_5S_3$: C, 57.62; H, 6.09; N, 4.98; Found: C, 58.1; H, 6.5; N, 4.6

Example 10

N-Butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-ethylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using ethylamine and acetyl chloride. The crude product in the final step was purified by LCMS (25% aqueous acetonitrile to 90% acetonitrile, reverse phase) to afford a colourless solid (18 mg, 46%).

IR (neat, cm^{-1}) ν 2960, 1747, 1627, 1463

^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 0.98 (d, 6.6 Hz, 6H), 1.08- 1.34 (m, 5H), 1.50 (m, 2H), 1.94 (m, 1H), 2.14 (m, 3H), 2.69 (m, 2H), 3.38 (m, 2H), 4.04 (m, 2H), 4.58 (m, 2H), 6.75 (m, 1H), 7.14- 7.60 (m, 4H)

^{13}C NMR ($CDCl_3$) δ 12.7, 13.6, 18.8, 21.2, 21.8, 22.2, 30.5, 39.3, 40.9, 42.9, 47.7, 51.3, 66.7, 66.8, 126.2, 127.7, 127.9, 129.2, 129.4, 130.9, 133.1, 133.4, 137.6, 138.4, 146.1, 150.4, 151.3, 151.5, 170.7

MS (ESI$^+$) m/z: 495.1 (M^+ +1)

Anal. Calcd for $C_{24}H_{34}N_2O_5S_2$: C, 58.27; H, 6.93; N, 5.66; Found: C, 58.7; H, 7.1; N, 5.8

Example 11

N-Butyloxycarbonyl-3-[4-(*N*-methanesulfonyl-*N*-methylaminomethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using methylamine and methanesulfonyl chloride. The crude product from the final step was purified by LCMS (35% aqueous acetonitrile to 70% acetonitrile, reverse phase) to afford a colourless syrup (40 mg, 59%).

IR (neat, cm^{-1}) ν 3208, 2960, 1749, 1458

^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 0.99 (d, J = 6.6 Hz, 6H), 1.25 (m, 2H), 1.50 (m, 2H), 1.94 (m, 1H), 2.71 (d, J = 7.3 Hz, 2H), 2.80 (s, 3H), 2.88 (s, 3H), 4.04 (t, J = 6.6 Hz, 2H), 4.34 (s, 2H), 6.77 (s, 1H), 7.35 (s, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H)

^{13}C NMR ($CDCl_3$) δ 13.6, 18.7, 22.2, 30.4, 30.5, 34.5, 36.0, 39.3, 53.5, 66.9, 128.2, 129.3, 129.4, 130.6, 133.8, 136.3, 146.0, 150.0, 151.7

MS (ESI$^+$) m/z: 517.2 (M^+ +1)

Example 12

N-Butyloxycarbonyl-3-{4-[*N*-(ethyloxycarbonyl)-*N*-methylaminomethyl]-phenyl}-5-*iso*-butylthiophene-2-sulfonamide

The title compound was synthesised as stated in the above general procedure using methylamine and ethyl chloroformate. The crude product from the

final step was purified by LCMS (45% to 75% aqueous acetonitrile, reverse phase) to afford a colourless oil (40 mg, 74%).

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 7.26 Hz), 0.98 (d, 6H, J = 6.60 Hz), 1.17- 1.30 (m, 5H), 1.49 (m, 2H), 1.94 (m, 1H), 2.70 (d, 2H, J = 7.26 Hz), 2.87 (s, 3H), 4.02 (t, 2H, J = 6.60 Hz), 4.18 (q, 2H, J = 7.26 Hz), 4.49 (s, 2H), 6.76 (s, 1H), 7.26 (m, 2H), 7.44 (d, 2H, J = 8.25 Hz)

^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.55, 14.70, 18.71, 22.21, 30.37, 30.47, 33.74, 34.27, 39.28, 52.11, 61.59, 66.79, 127.23, 127.59, 129.08, 129.44, 130.50, 133.03, 138.24, 146.18, 150.05, 151.45, 156.53, 157.0

IR (neat, cm^{-1}): ν 2960, 1750, 1678, 1465, 1348, 1222, 1158

MS (ESI^+): *m/z* at 511.3 (M^+ +1)

Anal. Calcd for $C_{24}H_{34}N_2O_6S_2$: C, 56.5; H, 6.7; N, 5.5; Found: C, 56.9; H, 7.1; N, 5.4

Example 13

N-Butyloxycarbonyl-3-[4-(*N*-methoxy-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

(a) 3-[4-(*N*-Methoxy-*N*-methylaminomethyl)phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

3-(4-Formylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-thiophene-2-sulfonamide (40 mg, 0.11 mmol, see Preparation A above), *N*-methoxymethylamine hydrochloride (23.4 mg, 0.22 mmol) and triethylamine (60 µL, 0.44 mmol) were dissolved in dichloroethane charged with molecular sieves (4Å, 200 mg) under a N_2 atmosphere. $NaBH(OAc)_3$ (46 mg, 0.22 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. A second portion of the three reagents (1 eq.) were then added and the reaction mixture was stirred overnight. The reaction was quenched with $NaHCO_3$ (1 mL, satd.) and diluted with ethyl acetate (10 mL). The contents were poured into diatomaceous earth (liquid-

liquid extraction cartridge) in a polypropylene column (packed for 1.5 cm, 24 mL size) and eluted with ethyl acetate (30 mL). Concentration under vacuum afforded the crude product, which was then purified using circular chromatography (40% ethyl acetate in petroleum ether).

(b) *N*-Butyloxycarbonyl-3-[4-(*N*-methoxy-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

The product from step (a) was treated in accordance with Steps 3 and 4 of the General Procedure for Examples 1 to 12. The crude product was purified by LCMS (45% to 85% aqueous acetonitrile) to afford pure title product as a colourless solid (36 mg, 79%).

mp 101-102°C

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 7.26 Hz), 0.98 (d, 6H, J = 6.60 Hz), 1.25 (m, 2H), 1.49 (m, 2H), 1.95 (m, 1H), 2.64 (s, 3H), 2.71 (d, 2H, J = 6.93 Hz), 3.40 (s, 3H), 3.81 (s, 2H), 4.02 (t, 2H, J = 6.60 Hz), 6.78 (s, 1H), 7.43 (m, 4H)

^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.57, 18.73, 22.23, 30.37, 30.52, 39.30, 44.82, 59.93, 64.22, 66.87, 128.71, 129.45, 130.47, 133.04, 138.14. 146.32. 149.91, 151.47

IR (neat, cm^{-1}): ν 2958, 1751, 1436, 1347, 1159, 1047

MS (ESI^+): *m/z* at 469 (M^++1)

Anal. Calcd for $C_{22}H_{32}N_2O_5S_2$: C, 56.4; H, 6.9; N, 6.0; Found: C, 56.8; H, 7.1; N, 5.7

Example 14

N-Butyloxycarbonyl-3-[4-(*N*-formyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

(a) 3-[4-(*N*-Formyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

A mixture of 3-[4-(*N*-methylaminomethyl)phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (25 mg, 0.0063 mmol, prepared according to Step 1 of the General Procedure for Examples 1 to 12, using methylamine as the amine) and ammonium formate (120 mg, 1.9 mmol) in CH_3CN (1.5 mL) was refluxed for 12 hours, cooled and evaporated. The residue was directly loaded into a circular chromatography apparatus and eluted with 50% ethyl acetate in petroluem ether to afford the pure sub-title compound as a colourless solid (25 mg, 94%).

(b) *N*-Butyloxycarbonyl-3-[4-(*N*-formyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

40 mg of 3-[4-(*N*-formyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (40 mg, 0.12 mmol, see step (a) above) was then treated in accordance with Steps 3 and 4 of the General Procedure for Examples 1 to 12. The crude product was purified by LCMS (35% to 75% aqueous acetonitrile) to afford pure title product as a colourless syrup (34 mg, 77%).

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 7.26 Hz), 0.98 (d, 6H, J = 6.60 Hz), 1.24 (m, 2H), 1.50 (m, 2H), 1.94 (m, 1H), 2.69 (d, 2H, J = 6.93 Hz), 2.78 & 2.86 (s, 3H), 4.04 (td, 2H, J = 2.31 Hz, J = 6.60 Hz), 4.42 (s, 1H), 4.53 (s, 1H), 6.76 (d, 1H, J = 2.97 Hz), 7.26 (t, 2H, J = 7.92 Hz), 7.47 (t, 2H, J = 7.92 Hz), 8.11 & 8.23 (s, 1H), 8.6- 8.9 (br m, 1H)

^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.58, 18.71, 22.20, 29.60, 30.41, 30.47, 34.31, 39.25, 47.55, 53.27, 66.69, 126.79, 127.26, 128.03, 129.29, 129.45,

130.96, 133.53, 133.90, 136.10, 136.26, 145.64, 145.74, 150.42, 151.30, 151.46, 163.06

IR (neat, cm^{-1}): v 2960, 1746, 1662, 1466, 1346, 1158

MS (ESI^+): *m/z* at 467 (M^++1)

Anal. Calcd for $C_{22}H_{30}N_2O_5S_2$: C, 56.63; H, 6.48; N, 6.0; Found: C, 56.7; H, 6.5; N, 6.0

Example 15

N-Butyloxycarbonyl-3-[4-(*N*-acetylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide

(a) 3-[4-(*N*-Acetylaminomethyl)phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

To a nitrogen-flushed solution of $Pd(OAc)_2$ (17.5 mg, 0.078 mmol) in DME (2 mL), was added triphenylphosphine (82 mg, 0.312 mmol). The solution was flushed with nitrogen again and stirred under a N_2 atmosphere for 30 minutes. The brownish suspension was transferred to a nitrogen-flushed mixture of 5-*iso*-butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (0.50 g, 1.56 mmol, see Preparation A, step (c)), *N*-(4-bromobenzyl)acetamide (0.71 g, 3.12 mmol, prepared form 4-bromobenzylamine and acetyl chloride), and potassium carbonate (0.86 g, 6.24 mmol) in DME:H_2O:EtOH (3.5:1.5:1 mL). The mixture was refluxed overnight under a N_2 atmosphere, washed with aqueous NaOH solution (1M), water and brine, dried over anhydrous $MgSO_4$ and concentrated to afford the residue which was purified by circular chromatography (50% acetone in pet. ether) to afford pure sub-title product as a colourless solid (0.43 g, 65%).

mp 171-172°C

^1H NMR (270 MHz, $CDCl_3$): δ 0.97 (d, 6H, *J* = 6.60 Hz), 1.0 (s, 9H), 1.91 (m, 1H), 2.07 (s, 3H), 2.67 (d, 2H, J = 6.93 Hz), 4.47 (d, 2H, J = 5.61 Hz),

6.20 (br s, 1H), 6.73 (s, 1H), 7.37 (d, 2H, J = 7.92 Hz), 7.53 (d, 2H, J = 7.92 Hz)

^{13}C NMR (67.5 MHz, $CDCl_3$): δ 22.13, 23.21, 29.48, 30.50, 39.16, 43.28, 54.51, 127.76, 128.94, 129.25, 133.88, 136.11, 138.61, 143.14, 148.53, 170.18

IR (neat, cm^{-1}): ν 3314, 2963, 1650, 1535, 1432, 1308, 1136, 1049, 1009, 844

MS (ESI^+): *m/z* at 423.1 (M^++1)

Anal. Calcd for $C_{21}H_{30}N_2O_3S_2$: C, 58.44; H, 7.24; N, 6.49; Found: C, 58.1; H, 7.0; N, 6.5

(b) *N*-Butyloxycarbonyl-3-[4-(*N*-acetylaminomethyl)phenyl]-5-*iso*-butyl-thiophene-2-sulfonamide

3-[4-(*N*-Acetylaminomethyl)phenyl]-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (40 mg, 0.90 mmol, see step (a) above) was treated in accordance with Steps 3 and 4 of the General Procedure of Examples 1 to 12 above. The crude product was purified by LCMS (40% aqueous acetonitrile) to afford the pure title product as a colourless solid (31 mg, 70%).

mp 171-173°C

^{1}H NMR (270 MHz, CD_3COCD_3+D_20): δ 0.84 (t, 3H, *J* = 7.26 Hz), 0.95 (d, 6H, *J* = 6.60 Hz), 1.24 (m, 2H), 1.46 (m, 2H), 1.87- 2.02 (m, 4H), 2.75 (d, 2H, J = 7.26 Hz), 3.56 (br S, 2H), 3.97 (t, 2H, J = 6.27 Hz), 4.38 (s, 2H), 6.92 (s, 1H), 7.32 (d, 2H, J = 8.25 Hz), 7.47 (d, 2H, J = 8.25 Hz)

^{13}C NMR (67.5 MHz, CD_3COCD_3+D_20): δ 12.53, 18.04, 21.03, 21.40, 29.86, 38.04, 41.79, 65.21, 126.19, 126.67, 128.52, 129.15, 131.33, 132.22, 139.23, 145.03, 149.78, 150.37, 169.69, 205.98

IR (neat, cm^{-1}): ν 2954, 2496, 1748, 1612, 1458, 1352, 1297, 1150, 1039, 816, 578

MS (ESI^+): *m/z* at 467.0 (M^++1)

Anal. Calcd for $C_{22}H_{30}N_2O_5S_2.1/3\ H_20$: C, 55.91; H, 6.54; N, 5.93; Found: C, 55.9; H, 6.6; N, 5.9

Example 16

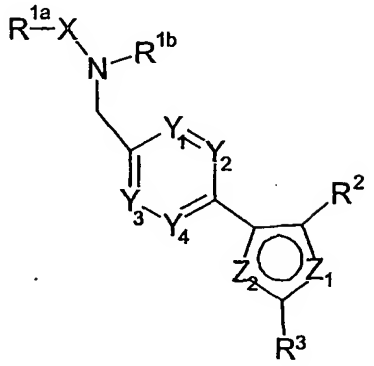
Title compounds of the Examples were tested in Tests A and B above and were found to exhibit an affinity for AT2 receptors of less than Ki = 50 nM and an affinity for AT1 receptors of Ki = 1 μM or greater.

Example 17

Title compounds of the Examples are tested in Test C above and are found to stimulate markedly mucosal alkalisation. This effect is blocked by co-administration of the selective AT2 receptor antagonist PD123319 (Sigma Chemical Company).

Claims

1. A compound of formula I,



I

wherein

X represents –O-, –C(O)- or –$S(O)_2$-;

R^{1a} and R^{1b} independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, Ar^1, Het^1, C_{1-3} alkyl-Ar^2, C_{1-3} alkyl-Het^2, C_{1-3} alkoxy-Ar^3 or C_{1-3} alkoxy-Het^3; or, in the case where X represents –C(O)- , R^{1a} may also represent C_{1-6} alkoxy or –O-Ar^4;

Ar^1, Ar^2, Ar^3 and Ar^4 each independently represent a C_{6-10} aryl group, which group is optionally substituted by one or more substituents selected from =O, -OH, cyano, halo, nitro, C_{1-6} alkyl (optionally terminated by -N(H)C(O)OR^{11a}), C_{1-6} alkoxy, phenyl, -N(R^{12a})R^{12b}, -C(O)R^{12c}, -C(O)OR^{12d}, -C(O)N(R^{12e})R^{12f}, -N(R^{12g})C(O)R^{12h}, -N(R^{12i})C(O)N(R^{12j})R^{12k}, -N(R^{12m})$S(O)_2R^{11b}$,-$S(O)_nR^{11c}$, -$OS(O)_2R^{11d}$ and -$S(O)_2$N(R^{12n})R^{12p};

Het^1, Het^2 and Het^3 each independently represent a four- to twelve-membered heterocyclic group containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group is optionally substituted by one or more substituents selected from =O, -OH, cyano, halo, nitro, C_{1-6} alkyl (optionally terminated by -N(H)C(O)OR^{11a}), C_{1-6} alkoxy, phenyl, -N(R^{12a})R^{12b}, -C(O)R^{12c}, -C(O)OR^{12d}, -C(O)N(R^{12e})R^{12f},

$-N(R^{12g})C(O)R^{12h}$, $-N(R^{12i})C(O)N(R^{12j})R^{12k}$, $-N(R^{12m})S(O)_2R^{11b}$, $-S(O)_nR^{11c}$, $-OS(O)_2R^{11d}$ and $-S(O)_2N(R^{12n})R^{12p}$;

R^{11a} to R^{11d} independently represent C_{1-6} alkyl;

R^{12a} to R^{12p} independently represent H or C_{1-6} alkyl;

n represents 0, 1 or 2;

Y_1, Y_2, Y_3 and Y_4 independently represent –CH- or -CF-;

Z_1 represents –CH-, -O-, -S-, -N- or -CH=CH-;

Z_2 represents –CH-, -O-, -S- or –N-;

provided that:

(a) Z_1 and Z_2 are not the same;

(b) when Z_1 represents –CH=CH-, then Z_2 may only represent –CH- or –N-; and

(c) other than in the specific case in which Z_1 represents –CH=CH-, and Z_2 represents –CH-, when one of Z_1 and Z_2 represents –CH-, then the other represents –O- or –S-;

R^2 represents $-S(O)_2N(H)C(O)R^4$, $-S(O)_2N(H)S(O)_2R^4$, $-C(O)N(H)S(O)_2R^4$, or, when Z_1 represents –CH=CH-, R^2 may represent $-N(H)S(O)_2N(H)C(O)R^5$ or $-N(H)C(O)N(H)S(O)_2R^5$;

R^3 represents C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkoxy-C_{1-6}-alkyl;

R^4 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino or di-C_{1-6} alkylamino; and

R^5 represents C_{1-6} alkyl,

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein R^{1a} and R^{1b} independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, Ar^1, Het^1, C_{1-3} alkyl-Ar^2, C_{1-3} alkyl-Het^2, C_{1-3} alkoxy-Ar^3 or C_{1-3} alkoxy-Het^3.

3. A compound as claimed in Claim 1 wherein, when X represents –C(O)-, then R^{1a} does not represent –O-Ar^4.

4. A compound as claimed in Claim 1 or Claim 2 wherein R^{1a} represents H, C_{1-5} alkoxy, C_{1-5} alkyl, Ar^1 or Het^1.

5. A compound as claimed in Claim 4, wherein R^{1a} represents H, C_{1-3} alkoxy, C_{1-4} alkyl, phenyl or thiophenyl.

6. A compound as claimed in any one of the preceding claims, wherein R^{1b} represents H, C_{1-4} alkyl, phenyl (optionally substituted by one or more C_{1-2} alkyl groups), C_{1-2} alkylphenyl, C_{1-2} alkyl-Het^2 or C_{1-2} alkoxy-C_{1-2}-alkyl.

7. A compound as claimed in Claim 6, wherein R^{1b} represents H, C_{1-3} alkyl, phenyl (optionally substituted by one or more methyl groups), benzyl or methylpyridinyl.

8. A compound as claimed in any one of the preceding claims, wherein X represents –O- or –C(O)-.

9. A compound as claimed in any one of the preceding claims, wherein Y_1, Y_2, Y_3 and Y_4 all represent –CH-.

10. A compound as claimed in any one of the preceding claims, wherein Z_1 represents -S- or –CH=CH-.

11. A compound as claimed in Claim 10, wherein Z_1 represents -S-.

12. A compound as claimed in any one of the preceding claims, wherein Z_2 represents –CH-.

13. A compound as claimed in any one of the preceding claims, wherein R^3 represents *n*-butyl or *iso*-butyl.

14. A compound as claimed in any one of the preceding claims, wherein, when R^2 represents $S(O)_2N(H)C(O)R^4$, $-S(O)_2N(H)S(O)_2R^4$ or $-C(O)N(H)S(O)_2R^4$, R^4 represents *n*-butyl, *n*-butoxymethyl, *iso*-butoxy or *n*-butoxy.

15. A compound as claimed in any one of the preceding claims, wherein R^2 represents $-S(O)_2N(H)C(O)R^4$.

16. A compound as claimed in Claim 15 wherein R^4 represents *n*-butoxymethyl, *iso*-butoxy or *n*-butoxy.

17. A compound as claimed in Claim 1, which is:
N-butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-benzylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-[4-(*N*-benzylpentylamidomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-[4-(*N*-*p*-tolylbenzylamidomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-*p*-tolylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-{4-[*N*-(pyridin-3-ylmethyl)benzylamidomethyl]-phenyl}-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-pyridin-3-ylmethylaminomethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-[4-(N-methylpentylamidomethyl)phenyl]-5-iso-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(*N*-ethyl-thiophenecarbonylaminomethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(*N*-acetyl-*N*-ethylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(*N*-methanesulfonyl-*N*-methylaminomethyl)-phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-{4-[*N*-(ethyloxycarbonyl)-*N*-methylaminomethyl]-phenyl}-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(*N*-methoxy-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(*N*-formyl-*N*-methylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide; or

N-butyloxycarbonyl-3-[4-(*N*-acetylaminomethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide.

18. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

19. A compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

20. A compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

21. A compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which endogenous production of AngII is deficient.

22. A compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which an increase in the effect of AngII is desired or required.

23. A compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

24. The use of a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

25. The use of a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which endogenous production of AngII is deficient.

26. The use of a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which an increase in the effect of AngII is desired or required.

27. The use of a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, for the manufacture of a

medicament for the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

28. The use as claimed in any one of Claims 24 to 27, wherein the condition is of the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system, or the central nervous system.

29. The use as claimed in Claim 28, wherein the condition is oesophagitis, Barrett's oesophagus, a gastric ulcer, a duodenal ulcer, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, hepatic disorders (including hepatitis), gall bladder disease, multiple organ failure, sepsis, xerostomia, gastritis, gastroparesis, hyperacidity, a disorder of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion, Sjögren's syndrome, inflammatory disorders, asthma, an obstructive lung disease (including chronic obstructive lung disease), pneumonitis, pulmonary hypertension, adult respiratory distress syndrome, renal failure, nephritis, renal hypertension, diabetic retinopathy, premature retinopathy, retinal microvascularisation, ovulatory dysfunction, hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post baloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, angina, cardiac arrhythmias, claudicatio intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic lesions, erectile dysfunction, neointima proliferation, cognitive dysfunctions, dysfunctions of food intake (hunger/satiety), thirst, stroke, cerebral bleeding, cerebral embolus, cerebral infarction, hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, an ulcer, adipose tissue hyperplasia, stem cell

differentiation and proliferation, cancer, apoptosis, tumours, hypertrophy diabetes, neuronal lesions or organ rejection.

30. The use as claimed in Claim 29, wherein the condition is non-ulcer dyspepsia, irritable bowel syndrome, multiple organ failure, hypertension or cardiac failure.

31. A method of treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

32. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

33. A kit of parts comprising components:

(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

34. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, and an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. A kit of parts comprising components:

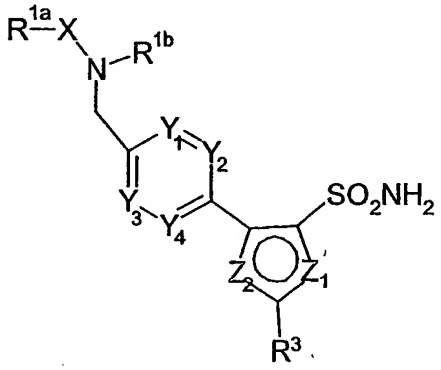
(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

36. A process for the preparation of a compound as defined in Claim 1, which comprises:

(i) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ or $-S(O)_2N(H)S(O)_2R^4$, and R^4 is as defined in Claim 1, reaction of a compound of formula II,



II

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as defined in Claim 1 with a compound of formula III,

R^4GL^1 III

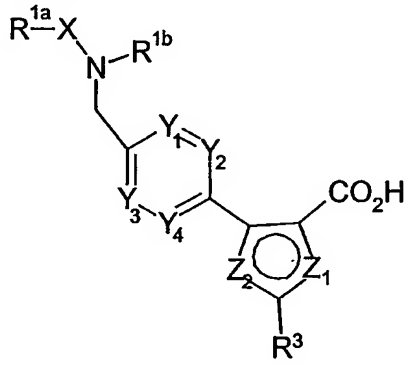
wherein G represents C(O) or $S(O)_2$ (as appropriate), L^1 represents a suitable leaving group and R^4 is as defined in Claim 1;

(ii) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents C_{1-6} alkoxy-C_{1-6}-alkyl, coupling of a compound of formula II as defined above with a compound of formula IV,

$R^{4a}CO_2H$ IV

wherein R^{4a} represents C_{1-6} alkoxy-C_{1-6}-alkyl;

(iii) for compounds of formula I in which R^2 represents $-C(O)N(H)S(O)_2R^4$ and R^4 is as defined in Claim 1, coupling of a compound of formula V,



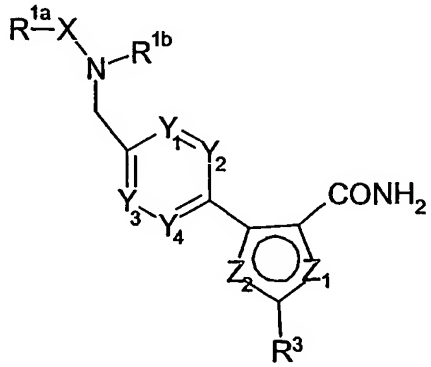
V

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as defined in Claim 1 with a compound of formula VI,

$R^4S(O)_2NH_2$ VI

wherein R^4 is as defined in Claim 1;

(iv) for compounds of formula I in which R^2 represents $-C(O)N(H)S(O)_2R^4$ and R^4 is as defined in Claim 1, coupling of a compound of formula VII,



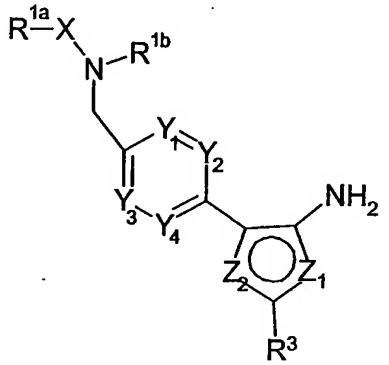
VII

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as defined in Claim 1 with a compound of formula VIII,

$$R^4S(O)_2Cl \qquad \text{VIII}$$

wherein R^4 is as defined in Claim 1;

(v) for compounds of formula I in which R^2 represents $-N(H)S(O)_2N(H)C(O)R^5$ and R^5 is as defined in Claim 1, reaction of a compound of formula IX,



IX

wherein R^{1a}, R^{1b}, X, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^3 are as defined in Claim 1 with a compound of formula X,

$$R^5C(O)N(H)S(O)_2Cl \qquad \text{X}$$

wherein R^5 is as defined in Claim 1;

(vi) for compounds of formula I in which R^2 represents $-N(H)C(O)N(H)S(O)_2R^5$ and R^5 is as defined in Claim 1, reaction of a compound of formula IX as defined above with a compound of formula XI,

$$R^5S(O)_2N(H)C(O)OR^x \qquad \text{XI}$$

wherein R^x represents C_{1-2} alkyl and R^5 is as defined in Claim 1;

(vii) for compounds of formula I in which R^2 represents $-N(H)C(O)N(H)S(O)_2R^5$ and R^5 is as defined in Claim 1, reaction of a compound of formula IX as defined above with a compound of formula XII,

$$R^5S(O)_2NCO \qquad \text{XII}$$

wherein R^5 is as defined in Claim 1;

(viii) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents C_{1-6} alkylamino, reaction of a compound of formula II as defined above with a compound of formula XIII,

$$R^{4b}NCO \qquad XIII$$

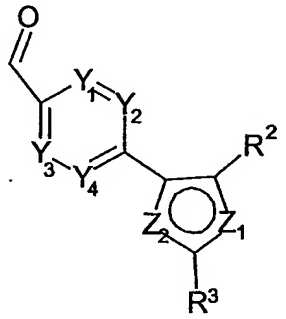
wherein R^{4b} is C_{1-6} alkyl;

(ix) for compounds of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents di-C_{1-6} alkylamino, reaction of a corresponding compound of formula I in which R^2 represents $-S(O)_2N(H)C(O)R^4$ and R^4 represents C_{1-6} alkoxy with a compound of formula XIIIa,

$$R^{4c}N(H)R^{4d} \qquad XIIIa$$

wherein R^{4c} and R^{4d} independently represent C_{1-6} alkyl; or

(x) for compounds of formula I in which X represents O, reductive amination of a compound of formula XIV,



XIV

wherein Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, R^2 and R^3 are as defined in Claim 1, in the presence of a compound of formula XV,

$$R^{1a}ONHR^{1b} \qquad XV$$

wherein R^{1a} and R^{1b} are as defined in Claim 1.

37. A compound of formula II as defined in Claim 36 or a protected derivative thereof, provided that when Z_1 represents –CH=CH-, then Z_2 does not represent –CH-.

38. A compound of formula II as defined in Claim 36, or a protected derivative thereof, wherein Z_1 represents –S- and Z_2 represents –CH-.

39. A compound of formula V as defined in Claim 36 or a protected derivative thereof.

40. A compound of formula VII as defined in Claim 36 or a protected derivative thereof.

41. A compound of formula IX as defined in Claim 36 or a protected derivative thereof.

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/GB 03/01251

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D333/34 C07D409/12 C07D333/38 A61K31/381 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal; WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 68226 A (AVENTIS PHARMA GMBH) 16 November 2000 (2000-11-16) cited in the application claims	1-41
A	WO 01 44239 A (BRISTOL MYERS SQUIBB CO ;MURUGESAN NATESAN (US); GU ZHENGXIANG (US) 21 June 2001 (2001-06-21) cited in the application claims	1-41
P,A	WO 02 072569 A (AVENTIS PHARMA GMBH) 19 September 2002 (2002-09-19) cited in the application claims	1-41

-/-

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2003	14/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ıal Application No
PCT/GB 03/01251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 096883 A (MCNEENEY STEPHEN PHILLIP ;HALLBERG ANDERS (SE); ALTERMAN MATHIAS () 5 December 2002 (2002-12-05) cited in the application claims	1-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/01251

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-23, 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB 03/01251

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